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Previews

Capitalizing on Deep Brain Stimulation: Thalamus as a Language Monitor

Thomas F. Münte[1,2] and Marta Kutas[3,4,*]
[1]Department of Neuropsychology
[2]Center for Behavioral Brain Sciences
Otto-von-Guericke University, 39106 Magdeburg, Germany
[3]Department of Cognitive Science
[4]Center for Research in Language
University of California, San Diego, La Jolla, CA 92093, USA
*Correspondence: mkutas@ucsd.edu
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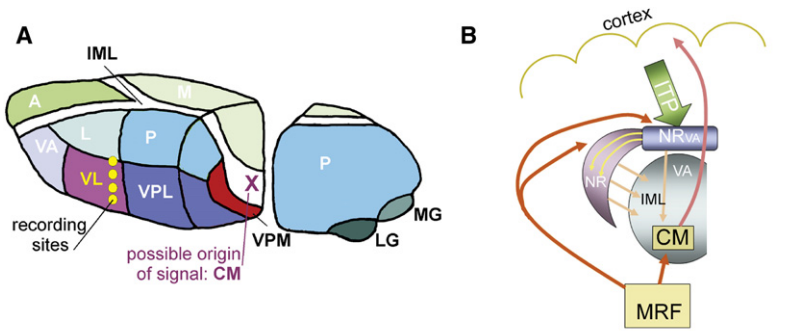
In this issue of *Neuron,* Wahl et al. demonstrate via invasive recordings from Deep Brain Stimulation leads that the thalamus (but not basal ganglia) is sensitive to certain linguistic violations, consistent with a subcortical role in selective recruitment of language-related cortical areas.

Phylogenetically, language processing is one of the latest additions to the human behavioral repertoire. This might suggest that language functions should be served by the newer (cortical) regions of the human brain, and, indeed, cortical areas along the sylvian fissure in the left hemisphere have long been presumed to be the seat of language. Whereas the specific roles assigned to left perisylvian regions and to the right hemisphere more generally have changed, owing to the phenomenal advances in cognitive neuroscience in the past decades (Hagoort, 2005), the cortico-centric view of language has not. As early as 1959, Penfield and Roberts alluded to the ''integrative'' language functions of the thalamus in *Speech and Brain Mechanisms*. More recently, the thorough review of Nadeau and Crosson (1997) of the subcortical aphasias implicates the thalamus, but not the basal ganglia, in language processing. Brain imaging studies of language, likewise, indicate thalamic engagement during lexical retrieval and meaning acquisition (Mestres-Misse et al., 2008). Of course, the inferential logic of the lesion approach is known to be problematic, as is the low temporal resolution of functional (neuro)imaging. We thus await answers about the role of the thalamus in language processing: e.g., (1) what does it compute? (2) Which subregions do what? (3) From where do its inputs come, (4) to where do its outputs go, and (5) to what temporal constraints is it subject? Answers to questions of this sort clearly call for a more temporally and spatially precise look at the inner workings of the brain via electrophysiological methods.

An initial glimpse is provided in this issue of *Neuron* by Wahl et al. (2008) via invasive electrophysiological recordings in awake humans that demonstrate that the electrical activity in the thalamus, but not in the basal ganglia circuit, is sensitive to semantic and syntactic linguistic violations, and by inference demonstrate that the thalamus is involved in language processing. Wahl et al. capitalized on the increasing use over the past 10 years of Deep Brain Stimulation (DBS) of subcortical brain structures for the alleviation of certain neuropsychiatric disorders. Critically, recordings from DBS electrodes offer a means for assessing the contribution or contributions of subcortical structures to cognition with exquisite temporal resolution (Münte et al., 2008a).

To assess the role of the basal ganglia (STN and GPi) and thalamus (VIM) in language, Wahl et al. (2008) recorded electrical brain activity from more than 20 patients. Recordings were made simultaneously from DBS electrode contacts in these target structures and surface (scalp) EEG electrodes as these patients listened to German sentences, half of which ended with a semantic violation (e.g., *The bread was polished.*) or a syntactic violation (*The bread was in eaten.*). Compared with the reaction to the final words of correct sentences (*The bread was eaten.*), averaged scalp event-related brain potentials (ERPs) to violations showed characteristic responses: semantic violations elicited an N400 and syntactic violations elicited an early left anterior negativity (ELAN) followed by a posterior positivity (P600) (Kutas et al., 2005). By contrast, neither the STN nor the GPi recordings showed any sensitivity to either type of linguistic violation, suggesting no basal ganglia participation. Thalamic contacts however showed distinctly different, reliable responses to both semantic *and* syntactic violations, but only if the activity of a thalamic contact was referenced to an electrode outside the skull (behind the ear) and not if both contacts were intrathalamic (see Figure 1A). According to Wahl et al., these findings imply that the language-related ERPs were not generated in the target structure per se; they argue for a probable generator in the centromedian area, embedded in the posterior limb of the internal medullary lamina (see Figure 1A) of the thalamus. In fact, most stroke victims with thalamic aphasia have damage to this richly interconnected (especially to frontal regions) area. The frontal lobe / inferior thalamic peduncle / nucleus reticularis / centromedian system is involved in the modulation of attentional processes, and damage to this ''selective engagement mechanism'' (Nadeau and Crosson, 1997) may lead to thalamic aphasia (Figure 1B). It is intriguing to speculate that the intracranial potentials recorded by Wahl et al. may be the electrophysiological signature of such a selective engagement mechanism.

At a minimum, recordings from within the putative generator (centromedian



nuclei: A=anterior, L=lateral, M=medial, VA=ventral anterior,VL=ventral lateral, VPL=ventral posterior lateral, VPM=ventral posterior medial, P=pulvinar, LG=lateral geniculate, MG=medial geniculate, CM=center median, IML=internal medullary lamina, NR=reticular nucleus, MRF=mesencephalic reticular formation, ITP=inferior thalamic peduncle

Figure 1. Thalamus and Selective Engagement

(A) Recording electrode with four contacts (yellow circles) in Wahl et al. (2008) located in the ventral lateral (VL) nucleus of which the ventral intermediate nucleus (VIM) forms the posterior and ventral portion. Because bipolar recordings between any combination of these contacts yielded no language-related modulations while those against an extracranial reference did, language-related signals were presumed to emanate from a nearby intrathalamic source—centromedian (CM) nucleus (marked by X).

(B) Selective engagement model schematic (Nadeau and Crosson, 1997). Information flows from cortex to the reticular nucleus (NR) of the thalamus via the inferior thalamic peduncle. The NR influences other parts of the thalamus, especially the CM, which in turn influences cortex. Future research will reveal whether this potential mechanism for selective engagement of cortical areas for language processing was the source of activity recorded by Wahl et al.

nucleus) are needed to substantiate such a relationship. This is a reasonable expectation given that the centromedian-parafascicular area of the thalamus has been successfully targeted for the treatment of pharmaco-resistant epilepsy and severe pain syndromes (Weigel and Krauss, 2004). Also critical for Wahl et al.'s hypothesis is delineating the precise temporal relationship between the depth and surface potentials: a selective engagement mechanism implicates a cortical/subcortical/cortical sequence, i.e., initial (presumably cortical) detection of the violation triggering thalamic activity, which in turn recruits cortical areas for reanalysis, repair, or both. Trial-by-trial comparisons of intracranial and surface activity latencies (Münte et al., 2008b) have nicely illustrated how such an analysis can establish the direction of information flow. Wahl et al. (2008) observed no peak-surface-to-depth latency differences for their semantic effects, but these analyses were of averaged (not individual trial) potentials, which when combined with the use of auditory inputs, may have caused temporal smearing, yielding no clearly defined ERP peak. By contrast, the relative time courses of the surface-to-depth syntactic effects were compatible with the time line sketched above, with a frontal surface negativity leading the initial thalamic response and a P600 component trailing the thalamic activity. Critically, however, this might be due to the fact that words *prior* to Wahl et al.'s syntactic violations (preposition) systematically differed from those prior to the violation controls (auxiliary verbs), and this may partially if not completely account for the extremely short onset latency of the scalp LAN. Accordingly, the timing results of Wahl et al., crucial for the selective engagement account, await replication with other types of syntactical violations (e.g., of number or tense).

The sequence of events (cortex → thalamus → cortex) postulated by the selective engagement model of language and suggested by the syntactic effects in Wahl et al. square with current views of thalamic functioning (Guillery and Sherman, 2002), according to which thalamic nuclei engage in "first-order" relaying of information from ascending pathways to cortical areas as well as "higher-order" routing between cortical areas. Many of these higher-order relay nodes apparently have modulatory functions that could adapt cortico-cortical information flow to current attentional demands. Assessing this directed information flow for language processing via intracranial recordings as in Wahl et al., or via functional connectivity analysis in conjunction with brain imaging (Rogers et al., 2007), is a worthy enterprise.

More generally, the report by Wahl et al. underscores the untapped utility of intracranial recordings to inform open issues in cognitive neuroscience. In domains ranging from motor control to memory to motivation, many contemporary models include some loop between cortical areas and the subcortical areas regulating their behaviors. The joint analysis of local field potentials from depth electrodes and concomitant surface EEG affords neuroscientists an invaluable opportunity to characterize the function or functions of these subcortical-cortical circuits. In addition to averaged phase-locked activity as in Wahl et al., time-frequency analyses of these electrical signals can provide novel information about task-related changes in subcortical structures that often exhibit high-frequency oscillatory behavior (Münte et al., 2008b). Naturally, we must remain mindful of the limitations inherent in this approach. The choice of the DBS site is dictated strictly by clinical considerations, setting many subcortical areas off limits; like Wahl et al., we must sometimes be satisfied with recordings from structures nearby. Moreover, target areas are often selected because the patient's condition has led to a dysfunction of the very region that DBS is intended to normalize (Münte et al., 2008a), and little is known about the extent to which these disease-related activity changes alter task-dependent reactivity of the structures for cognitive operations. These problems notwithstanding, invasive recordings as in Wahl et al. (2008), especially within a multimodal imaging framework, will lead to a long-overdue shift from a cognitive neuroscience focus on the cortex to a more balanced cortical-subcortical view.

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A Time and a Place for Nkx2-1 in Interneuron Specification and Migration

Laura A.B. Elias,[1] Gregory B. Potter,[1] and Arnold R. Kriegstein[1,*]
[1]Institute for Regeneration Medicine, University of California San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143, USA
*Correspondence: kriegsteina@stemcell.ucsf.edu
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The homeobox transcription factor, *Nkx2-1*, plays multiple roles during forebrain development. Using restricted genetic ablation of *Nkx2-1*, in this issue of *Neuron*, Butt et al. show that *Nkx2-1* in telencephalic progenitors regulates interneuron subtype specification, while Nóbrega-Pereira et al. demonstrate that postmitotic *Nkx2-1* regulates migration and sorting of interneurons to the striatum or cortex by controlling the expression of the guidance receptor, Neuropilin-2.

Nkx2-1 Is a Multifunctional Transcription Factor

A single transcription factor can participate in multiple developmental events as cells progress down a particular neuronal lineage. For example, a specific transcription factor may specify neuronal fate in a progenitor cell and subsequently regulate processes such as migration or differentiation in a postmitotic neuron. Such distinct developmental roles have now been described for the homeobox transcription factor, *Nkx2-1*. *Nkx2-1* regulates the identity of neuronal progenitor cells, mediates neuronal subtype specification, and directs neuronal migration. *Nkx2-1* is expressed in the basal telencephalon as early as the 11 somite stage and maintains its expression in defined structural regions of the developing basal telencephalon including the septum, anterior entopeduncular area, and preoptic area as well as the medial ganglionic eminence (MGE), a subregion of the ventral embryonic germinal zones known as the ganglionic eminences (Sussel et al., 1999). Interestingly, unlike the *Dlx* homeobox transcription factors, which are expressed in the lateral ganglionic eminence (LGE), caudal ganglionic eminence (CGE), and MGE (Flames et al., 2007), *Nkx2-1* is absent from the LGE and CGE (Sussel et al., 1999), suggesting a specific role in MGE neurogenesis.

The observation that *Nkx2-1* is expressed in the MGE ventricular and subventricular progenitor zones as well as in postmitotic cells provided an early clue that *Nkx2-1* could play multiple roles in MGE neurogenesis (Sussel et al., 1999). In this issue of *Neuron,* Butt et al. (2008) and Nóbrega-Pereira et al. (2008) build upon our previous understanding of *Nkx2-1* by describing the critical role that *Nxk2-1* plays during distinct temporal windows in the regional specification of the ventral telencephalon, fate determination of MGE progenitors, and sorting and migration of MGE-derived cells.

Nkx2-1 Helps Determine Interneuron Subtype Identity

GABAergic interneurons are remarkably diverse and are subdivided by morphology, connectivity, electrophysiology, and the expression of molecular markers (Markram et al., 2004). The majority of cortical interneurons can be classified by largely nonoverlapping expression of parvalbumin (PV), calretinin (CR), and somatostatin (SST). Most cortical interneurons are generated in the MGE and CGE, and their fates are determined by the place and time of their specification. PV- and SST-expressing interneurons are generated first and arise primarily from the MGE, while CR- and VIP-expressing interneurons are born later and arise in the CGE (Butt et al., 2005; Fogarty et al., 2007). In this issue of *Neuron*, Butt et al. (2008) demonstrate that *Nkx2-1* controls the regional identity of MGE progenitors and influences the cell-fate specification of MGE-derived interneurons in a temporally defined manner.

Butt et al. (2008) use a conditional loss-of-function approach to determine the role of *Nkx2-1* in the specification of interneuron subtypes. Using a tamoxifen-inducible Cre recombinase under the control of the *Olig2* locus in combination